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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,566	09/30/2003	Matthew B. Wheeler	66-00A	8372
23713	7590	01/26/2006	EXAMINER	
GREENLEE WINNER AND SULLIVAN P C			CROUCH, DEBORAH	
4875 PEARL EAST CIRCLE			ART UNIT	
SUITE 200			PAPER NUMBER	
BOULDER, CO 80301			1632	

DATE MAILED: 01/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,566	WHEELER ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-5 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>1/21/04, 7/02/04</u> . | 6) <input type="checkbox"/> Other: ____. |

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Claims 1-5 are pending.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-4 are rejected under 35 U.S.C. 101 because they are drawn to nonstatutory subject matter. The claims encompass transgenic humans which is subject matter precluded by the PTO policy (1077 O.G. 24 April 21, 1987). Insertion of "nonhuman" before animal will overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic nonhuman mammal having a genome comprising a heterologous nucleic acid sequence encoding a growth factor and encoding α -lactalbumin operably linked to a mammary preferential promoter, where the descendants have a genome comprising a heterologous nucleic acid sequence encoding a growth factor and encoding α -lactalbumin operably linked to a mammary preferential promoter and the descendants express an increased amount of growth factor in their milk and an increased amount of α -lactalbumin in their milk as compared to control non-transgenic nonhuman mammals, does not reasonably provide enablement for transgenic humans or methods using transgenic humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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The claims as presently written do not require the descendents to have the transgenes in their genome. The only enablement is where the descendents do have the transgene in their genome. The specification provides no other guidance for the descendents to meet the requirement of the claims to express and increased amount of α -lactalbumin and growth factor in their milk.

The claims encompass transgenic humans. At the time of filing, the production of transgenic humans was unpredictable. Houdebine (2002) states transgenic animals exhibit mosaicism in expression due to the presence of retrotransposons in the vicinity of genes or transgenes (page 155, col. 1, parag. 2, lines 3-6). Ristevski states the integration of the transgene into genomic sites near silencers inhibits expression; inappropriate tissue expression and the inability to control copy number integration are problems with transgenesis (page 159, col. 1, parag. 2, lines 5-7; parag. 3, lines 1-4 and col. 2, lines 3-9). Houdebine (2000) states the level and specificity of transgene expression cannot easily be predicted because of the site of integration or the position effect (page 309, col. 2, parag. 3, line 1 to page 310, line 2). The specification does not provide guidance on overcoming these art recognized unpredictabilities of transgenesis when producing non-mammal animals and transgenic humans. Applicant can overcome this rejection by limiting the claims to "nonhuman mammal".

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 5 is to a method of increasing the volume of milk and growth factor content of milk in transgenic animal comprising providing a transgenic animal having

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a genome comprising a heterologous nucleic acid sequence encoding a growth factor gene and encoding α -lactalbumin operably linked to a mammary preferential promoter, where said transgenic animal expresses an increased amount of growth factor in its milk and an increased milk volume as compared to control non-transgenic animals.

The method is not enabled because there is no evidence of record that the disclosed double transgenic sows exhibited an increase in milk volume, although they did demonstrate an increased amount of human IGF-1 in their milk.

First, the claims encompass transgenic humans. These claims are not enabled for the reasons presented above, and repeated here.

The specification provides no guidance on obtaining increased milk production through transgenesis comprising sows that express both a heterologous α -lactalbumin and a growth factor. The theory, as stated by Bleck et al (1998) University of Illinois Swine Research Report, pages 29 and 30), is the overexpression of α -lactalbumin will result in the production of more lactose (page 30, parag. 1 and 2). The increase in lactose will increase the osmolarity of the milk causing more water to be transported into milk, thus increasing milk volume. However, the specification offers no evidence to support this theory. The art at the time of filing taught, in transgenic sows expressing bovine α -lactalbumin and human IGF-1, the overall all concentration of lactose did not change sufficiently to increase milk volume (Bleck (1998) J. Animal Sci., page 3077, col. 2, parag. 2, lines 4-10 (Bleck-a)). On day 0 of lactation, sows had 46% greater lactose concentration than nontransgenic sows but by d 5, the difference had disappeared (Bleck-a, page 3077, col. 1, lines 10-15). The end result was no increase in lactalbumin concentration, and, according to the theory, without an increase in lactalbumin concentration there would be no

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increase in milk volume. Should applicant have further evidence to support this theory, it should be submitted in the form of a declaration under 35 U.S.C. § 1.132.

Therefore at the time of the instant invention, the skilled artisan would have been required to perform an undue amount of experimentation without a reasonable expectation of success to implement the invention of claim 5.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bleck et al (1998) J. Animal Sci. 76, 3072-3078 (Bleck-a) and Bleck et al. (1998) J. Animal Sci. 76, Suppl. 1/J. Dairy Sci., Suppl. 1., page 213, abst 828 (Bleck-b).

Bleck-a teaches the production of transgenic pigs whose genome comprise bovine α -lactalbumin genomic sequence including the endogenous expression regulatory sequences and coding sequences operably linked to a DNA sequence encoding (page 3074, figure 1 and page 3075, figure 3 and col. 1, parag, 1, line 1 to page 3076, col. 1, line 1). Bleck-a offers motivation in stating that pigs expressing bovine α -lactalbumin began producing the protein in their milk at d 0 of lactation, whereas pigs begin expressing the endogenous pig α -lactalbumin later (page 3076, col. 2, lines 1-6). Thus the transgenic pigs expressed elevated levels of α -lactalbumin (page 3076, col. 2, parag. 2, lines 1-5). Bleck-a offers motivation in stating that the milk produced by these pigs contained a greater amount lactose, leading to faster

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growth a piglets, a desired effect for increasing the number of piglets born per sow per year (page 3077, col. 2, parag. 2 to page 3078, col. 1, line 6).

Bleck-b teaches transgenic pigs whose genome comprise bovine α -lactalbumin expression regulatory sequences operably linked to a DNA sequence encoding human insulin like growth factor I (lines 9-12). Bleck-b further teaches a transgenic boar has been mated and passed the transgene on to three female offspring (lines 14-19). Bleck-b provides motivation in stating that piglets fed insulin like growth factor for the first 14 days post partum had longer intestinal villi and higher lactase activity than piglets fed formula alone (lines 1-4).

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to breed a transgenic pig expressing human IGF, taught by Bleck-b with a transgenic pig expressing bovine α -lactalbumin, taught by Bleck-a given the motivation stated by Bleck-a and Bleck-b of improved piglet growth to have both growth enhancing agents in the milk of sows. Some descendents would obviously have the transgenes and demonstrate increased growth factor and α -lactalbumin in their milk. There was a reasonable expectation of success at the time of filing to achieve this.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 7:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

January 20, 2006